The recognition that epigenetic modifications of the abnormal HSC clones in MDS affect cell growth and apoptosis and are central to disease pathogenesis led to the therapeutic application of two DNA methyltransferase inhibitors (i.e., 5-azacytidine and decitabine) to the disease. These agents are hypothesized to reverse the abnormal hypermethylation and gene silencing in abnormal HSCs.

5-Azacytidine delays the time to leukemic transformation in two thirds of patients with transfusion-dependent MDS, decreases transfusion requirements, and improves quality of life compared with transfusion support alone. This agent is the only drug shown to significantly prolong overall survival of MDS patients, largely by delaying (but not preventing) the time of onset of acute leukemic transformation in a phase III clinical trial comparing 5-azacytidine with conventional care regimens for higher-risk MDS patients. These results are the first to demonstrate that any therapy can alter the natural history of this disease and renders 5-azacytidine the standard of care for transfusion-dependent MDS patients.

Decitabine is a compound related to 5-azacytidine and represents an alternative treatment option for patients with high-risk MDS. Decitabine therapy induces remission and reduces transfusion needs compared with supportive care and historical controls; however, the survival benefit of decitabine use in MDS has not been demonstrated.

A unique feature of DNA methyltransferase inhibitor therapy with either hypomethylating agent is that most therapeutic responses occur 4 to 6 months after treatment initiation. Moreover, MDS patients treated with 5-azacytidine who did not achieve a defined complete remission in the marrow still survived significantly longer than patients treated with supportive care alone. These data suggest that (unlike AML) the best treatment for MDS is not cytotoxic-mediated eradication of abnormal HSC clones but chronic (epigenetic) modification of cells resulting in restoration of normal hematopoiesis. It remains to be seen whether achievement of remission after hypomethylation modulation in MDS equates with long-term disease control.

Lenalidomide

Patients with lower-risk MDS characterized by deletions in the long arm of chromosome 5 (5q– aberration) typically have anemia with preserved platelet counts. Many have a disease subtype that is extraordinarily sensitive to therapy with lenalidomide, an immunomodulatory agent that exerts antigrowth effects on MDS cells and their surrounding marrow microenvironment. Complete and durable responses after lenalidomide therapy occur in up to 66% of 5q– syndrome MDS patients and are accompanied by disappearance of the abnormal cytogenetic clone in the marrow in some patients. Defects in ribosomal protein function, specifically the ribosomal subunit protein RPS14, have been identified as the cause of 5q– syndrome MDS, paralleling findings implicating a different ribosomal subunit (RPS19) in the congenital bone marrow syndrome Diamond-Blackfan anemia.

Studies have suggested that lenalidomide targets aberrant signaling pathways caused by haplosufficiency of specific genes in a commonly deleted region on chromosome 5 (i.e., *SPARC*, *RPS14*, *CDC25C*, and *PPP2CA*). The agent specifically targets del(5q) clones while also promoting erythropoiesis and repopulation of the bone marrow in normal cells. Lenalidomide induces responses in up to one third of non-5q– MDS patients, demonstrating a specific defect in erythroid differentiation on gene expression profiling.

Prognosis

Formulation of MDS prognostic categories remains a work in progress. In 1998, the IPSS was developed by an international working group to better predict clinical outcomes in MDS. The IPSS divides patients with MDS into three prognostic categories based on cytogenetic abnormalities, cytopenias, advanced age, and percentage of bone marrow blasts, and it provides median survival and time to leukemic transformation for each IPSS stage (Table 45-7).

Based on criticism that the IPSS relies only on characteristics of patients at disease onset and includes cases now considered to be AML by the World Health Organization (WHO) criteria, a new WHO classification–based prognostic scoring system (WPSS) was devised emphasizing WHO morphology, karyotype, and transfusion dependence at any time during the MDS disease course. Division of MDS patients into five new risk categories was validated to predict for overall survival and leukemic evolution for MDS at any follow-up time (see Table 45-6).

Combined data from multiple international databases, including 7012 MDS patients, were statistically analyzed and used to generate a new prognostic classification system for untreated MDS patients, the Revised International Prognostic Scoring System (R-IPSS). This model retained marrow cytogenetics (including several novel karyotypic abnormalities), marrow blast percentage, and cytopenias as clinically prognostic markers but divided patients into five, rather than three, prognostic categories (Table 45-8). Despite the advances made in predicting outcomes for MDS patients, all of these prognostic models are limited by their exclusion of molecular features, specifically gene mutations.

Modern genomic sequencing technologies have revolutionized biomedical investigation by allowing parallel assessment of

TABLE 45-7 INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC DISORDERS

SCORE	BLASTS	KARYOTYPE	CYTOPENIAS*	OVERALL SCORE	MEDIAN SURVIVAL (YR)
0	<5%	Normal, –Y, 5q–, 20q–	0-1 cytopenias	0	5.7
0.5	5-10%	All other abnormalities	2-3 cytopenias	0.5-1.0	3.5
1.0		Abnormal 7, >3 abnormalities		1.5-2.0	1.2
1.5	11-20%			2.5 or higher	0.4
2.0	21-30%				

*Cytopenias are defined as hemoglobin <10 g/dL, neutrophils <1500/μL, platelets <100,000/μL.